UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

IN RE: TYLENOL (ACETAMINOPHEN) MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	§	**MDL NO. 2436** **2:13-md-02436** **HON. LAWRENCE F. STENGEL**
This Document Relates to: Rana Terry, as Personal Representative and Administrator of the Estate of Denice Hayes, Deceased, Plaintiff, vs. McNEIL-PPC, Inc., McNeil Consumer Healthcare, and Johnson & Johnson, Inc., Defendants.	§	Civil Action No. 2:12-cv-07263

M E M O R A N D U M

Stengel, J. **July 26, 2016**

This case is part of a Multidistrict Litigation (MDL) involving claims of liver damage from the use of Tylenol at or just above the recommended dosage.[1] The first

[1] See Master Compl., 13-md-2436, Doc. No. 32. There are over two hundred other cases included in this MDL, along with several similar cases in New Jersey state court.

"bellwether" case is scheduled for trial.[2] The plaintiff plans to offer Dr. Timothy Davern, M.D. as a general and specific causation expert. Dr. Davern contends that recommended doses of acetaminophen, the main ingredient in Tylenol, can cause acute liver failure (ALF). He is of the opinion that the decedent, Denice Hayes, died of acetaminophen-induced ALF after taking recommended doses. The defendants move to exclude his testimony under Daubert. For the reasons stated below, I will deny their motion.[3]

I. LEGAL STANDARD

The admissibility of expert testimony is governed by Federal Rules of Evidence 702 and 703 as well as by Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), and its progeny.[4] See In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 735 (3d Cir. 1994). "Under the Federal Rules of Evidence, a trial judge acts as a 'gatekeeper' to ensure that 'any and all expert testimony or evidence is not only relevant, but also reliable.'" Pineda v. Ford Motor Co., 520 F.3d 237, 243 (3d Cir. 2008)(quoting Kannankeril v. Terminix Int'l, Inc., 128 F.3d 802, 806 (3d Cir. 1997)). The Third Circuit recognizes a "liberal policy of admissibility" regarding Rule 702. Pineda, 520 F.3d at 243

[2] A "bellwether" case is a test case. "Bellwether" trials should produce representative verdicts and settlements. The parties can use these verdicts and settlements to gauge the strength of the common MDL claims to determine if a global resolution of the MDL is possible. See FEDERAL JUDICIAL CENTER, MANUAL FOR COMPLEX LITIGATION, FOURTH EDITION 360 (2004); DUKE LAW CENTER FOR JUDICIAL STUDIES, MDL STANDARDS AND BEST PRACTICES 16-21 (2014).

[3] In making my decision, I have reviewed all of the materials submitted as attachments to the parties' briefs, including those submitted during oral argument.

[4] Daubert held that the Federal Rules of Evidence, specifically Rule 702, controlled the issue of when experts were qualified. Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 587-88 (1993). It found that Rule 702 superseded the Court's prior precedent on the subject found in Frye v. United States, 54 App.D.C. 46, 47, 293 F. 1013, 1014 (1923). Id. at 587. Daubert went on to clarify what was required under Rule 702, as compared to Frye. See id. at 589-598.

(quoting Kannankeril, 128 F.3d at 806); United States v. Schiff, 602 F.3d 152, 173 (3d Cir. 2010).[5]

"[B]ecause expert evidence is often more misleading than other evidence, Rule 403 gives a judge more power over experts than over lay witnesses." In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 747 (3d Cir. 1994). However, "in order for a district court to exclude scientific evidence, there must be something particularly confusing about the scientific evidence at issue—something other than the general complexity of scientific evidence." Id.

a. Rule 702

Federal Rule of Evidence 702 has three major requirements: 1) the expert must be qualified; 2) the expert must testify about matters requiring scientific, technical, or specialized knowledge; and 3) the testimony must assist the trier of fact.[6] Pineda, 520 F.3d at 243 (citing Kannankeril, 128 F.3d at 806). 702's inquiry should be a "flexible one." Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 594 (1993).

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[5] See also Holbrook v. Lykes Brothers Steamship Company, Inc., 80 F.3d 777, 780 (3d Cir. 1996); Zaprala v. USI Servs. Gp., Inc., No. 09–1238, 2013 WL 1148335, at *6 (E.D. Pa. Mar. 20, 2013)(quoting Pineda, 520 F.3d at 243).

[6] Federal Rule of Evidence 702 states:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and
>
> (d) the expert has reliably applied the principles and methods to the facts of the case.

FED. R. EVID. 702.

i. Expert Must Be Qualified

An expert's qualifications may include education, provided it is in a field related to the one in which the expert intends to testify. Fedor v. Freightliner, Inc., 193 F. Supp. 2d 820, 827 (E.D. Pa. 2002). Overall, the court will consider both academic training and practical experience to determine if the expert has "more knowledge than the average lay person" on the subject. Id. at 827-28 (citing Waldorf v. Shuta, 142 F.3d 601, 627 (3d Cir. 1998)). "An expert may be generally qualified but may lack qualifications to testify outside his area of expertise." Calhoun v. Yamaha Motor Corp., U.S.A., 350 F.3d 316, 322 (3d Cir. 2003).

However, this does not mean that the "best qualified" expert must testify. "[W]itnesses may be competent to testify as experts even though they may not, in the court's eyes, be the 'best' qualified." Holbrook v. Lykes Bros. S.S. Co., Inc., 80 F.3d 777, 782 (3d Cir. 1995).[7] "Rule 702 and Daubert put their faith in an adversary system designed to expose flawed expertise." U.S. v. Mitchell, 365 F.3d 215, 244-45 (3d Cir. 2004)(citations omitted). "As long as an expert's scientific testimony rests upon 'good grounds, based on what is known,' it should be tested by the adversary process—competing expert testimony and active cross–examination—rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or satisfactorily weigh its inadequacies." Id. at 244 (citations omitted).

[7] See also Keller v. Feasterville Family Health Care, 557 F. Supp. 2d 671, 675 (E.D. Pa. 2008)(Rice, J.).

ii. Expert's Methods Must be Reliable

This Circuit interprets the second factor as one of "reliability," i.e., the testimony is admissible so long as the process or technique the expert used in formulating the opinion is reliable. Pineda, 520 F.3d at 244. An expert's opinion need not be correct, only reliable. See In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 744 (3d Cir. 1994)("This does not mean that plaintiffs have to prove their case twice—they do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are *correct*, they only have to demonstrate by a preponderance of evidence that their opinions are reliable." (emphasis in original)). "[A]n expert is permitted wide latitude to offer opinions, including those that are not based on firsthand knowledge or observation." Daubert, 509 U.S. at 592. "[I]t is the burden of the party offering the expert scientific testimony to demonstrate reliability by a preponderance of the evidence." In re TMI Litig., 193 F.3d 613, 705 (3d Cir. 1999)(citing Paoli II, 35 F.3d at 744).[8]

"Rule 702 grants the district judge the discretionary authority, reviewable for its abuse, to determine reliability in light of the particular facts and circumstances of the particular case." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 158 (1999). Judges considering this factor should look to whether a theory, technique, or opinion can be tested or has been subject to peer review or publication. Daubert, 509 U.S. at 593. "The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant,

[8] See also FED. R. EVID. 702, Advisory Committee Note (2000 Amendments)("Under that Rule, the proponent has the burden of establishing that the pertinent admissibility requirements are met by a preponderance of the evidence." (citing Bourjaily v. United States, 483 U.S. 171 (1987)).

though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised." Id. at 594. A court should also consider the known or potential rate of error involved in a scientific method. Id. "Reliability" does not require that a technique or methodology be generally accepted by a scientific community. Id. See also id. at 597-98. However, "[w]idespread acceptance can be an important factor in ruling particular evidence admissible" while a minimally supported technique "may properly be viewed with skepticism." Id.

iii. Expert Must be Helpful

The third factor "is typically understood in terms of whether there is a sufficient 'fit' between the expert's testimony and the facts that the jury is being asked to consider." United States v. Schiff, 602 F.3d 152, 172-73 (3d Cir. 2010)(citing Daubert, 509 U.S. at 591). See also In re: TMI Litigation, 193 F.3d 613, 670 (3d Cir. 1999). This factor is about relevance. "Expert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful." Daubert, 509 U.S. at 591 (quoting 3 Weinstein & Berger ¶ 702[02], p. 702–18). "Rule 702's 'helpfulness' standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility." Id. at 591-92.

b. Rule 703

Under Federal Rule of Evidence 703, the data underlying the expert's opinion is the central focus. Rule 703 states:

> An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted. But if the facts or data would otherwise be inadmissible, the

> proponent of the opinion may disclose them to the jury only if their probative value in helping the jury evaluate the opinion substantially outweighs their prejudicial effect.

FED. R. EVID. 703. The trial court must evaluate whether the data used by an expert is reasonably relied upon by experts in the field. See In re Paoli RR Yard PCB Litigation (Paoli II), 35 F.3d 717, 747-49 (3d Cir. 1994).

I. Dr. Davern is a Leading Expert in DILI[9]

Timothy Davern, M.D. is a board-certified gastroenterologist and hepatologist, specializing in liver transplants. He is the Director of the Acute Liver Failure Program at California Pacific Medical Center (CPMC) in San Francisco, California. Prior to joining CPMC, he held several academic positions at University of California, San Francisco (UCSF), including Associate Professor of Medicine.

Dr. Davern is an active investigator for the Acute Liver Failure Study Group (ALFSG). He has been involved with the ALFSG for almost 15 years. He has personally enrolled nearly 300 ALFSG cases, most of which were due to acetaminophen toxicity. He represented the American Association for the Study of Liver Disease (AASLD) at the joint meeting of three Food and Drug Administration (FDA) Advisory Committees, held in June 2009. He presented data from the ALFSG on unintentional acetaminophen poisoning at that joint meeting. He was also the principal investigator for the National

[9] Though the defendants do not challenge Dr. Davern's qualifications, an overview of his credentials is helpful to understanding their challenge to his methodology. Information about Dr. Davern's credentials can be found in his Curriculum Vitae (Doc. No. 155, Ex. 6) and his expert report (Doc. No. 155, Ex. 1) unless noted otherwise. See also T. Davern Dep., Mar. 28, 2015 at 73-78 (Doc. No. 155, Ex. 3).

Institutes of Health (NIH)-funded Drug-Induced Liver Injury Network (DILIN) Study from its inception in 2004 until 2014.

Dr. Davern is a national-recognized expert in drug-induced liver injury (DILI).[10] He has published close to 100 articles, including peer-reviewed research, book chapters and abstracts—almost all of which have to do with acute liver failure (ALF), drug-induced liver disease, and acetaminophen-induced ALF.[11] He has conducted research related to acetaminophen-induced liver injury. In addition, he has written about the DILI

[10] Defendants' hepatology experts acknowledge Dr. Davern as a national-recognized expert in DILI. See R. Brown Dep., Apr. 30, 2015 at 41-43 (Doc. No. 155, Ex. 8); S. Flamm Dep., May 5, 2015 at 29-36 (Doc. No. 155, Ex. 9).

[11] See, e.g., Murphy, E.J., Davern, T.J., et al., Troglitazone Induced Fulminant Hepatic Failure: A Report of Three Case, Digestive Diseases and Sciences, 2000, 45(3):549-553; Ostapowicz, G., Davern, T.J., et al., Results of a Prospective Study of Acute Liver Failure at 17 Tertiary Care Centers in the United States, Annals of Internal Medicine, 2002, 137(12):947-954; Davern, T.J., Fulminant Hepatic Failure, in Advanced Therapy in Gastroenterology and Liver Disease, TM Bayless and AM Diehl, Eds., Fifth Edition, BC Decker, Inc., Ontario, at 629-637; Schiodt, F.V., Davern, T., et al., Viral Hepatitis Related Acute Liver Failure, Am. J. Gastroenterol., 2003, 98(2):448-453; Davern, T.J., Acetaminophen hepatotoxicity, Hepatology, 2004, 40(4): 1021-1022; Wai, C.T., Davern, T.J., et al., Clinical outcome and virological characteristics of hepatitis B-related acute liver failure in the United States, J. Viral. Hepat., 2005 Mar: 12(2):192-198; Vaquero, J., Davern, T.J., et al., Blei AT Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe Encephalopathy, Liver Transpl., 2005 Dec; 11(12):1581-1589; Larson, A.M., Davern, T.J., et al., Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, Hepatology, 2005 Dec: 42(6): 1364-1372; Davern, T.J., et al., Measurement of serum acetaminophen protein adducts in patients with acute liver failure, Gastroenterology, 2006 Mar.: 130(3):687-694; Rutherford, A., Davern, T.J., et al., High Body Mass Index Predicts Poor Outcome in Acute Liver Failure, Clin. Gastroenterol. & Hepatology, 2006 Sep 2; [Epub ahead of print]; Lee, W.M., Davern, T., et al., Brief Report: No Evidence for Parvovirus B19 or Hepatitis E Virus as Cause of Acute Liver Failure, Dig. Dis. Sci., 2006 Sep. 9 [Epub ahead of print]; James, L.P., Davern, T.J., et al., Detection of acetaminophen protein adducts in children with acute liver failure of indeterminate etiology, Pediatrics, 2006 Sep.: 118(3): e676-81; Stravitz, R.T., Davern, T., et al., Intensive care of patients with acute liver failure: Recommendations of the U.S. Acute Liver Failure Study Group, Crit. Care Med. 2007 Sep. 25, [Epub ahead of print]; Davern, T.J., Predicting prognosis in acute liver failure: ammonia and the risk of cerebral edema, Hepatology, 2007 Dec.: 46(6): 1679-1681; Chalasani, N., Davern, T.J., et al., Clinical Advances in Liver, Pancreas and Biliary Tract: Causes, Clinical Features and Outcomes from a Prospective Study of Drug-Induced Injury in the United States, Gastroenterology, 2008; 135:1924-1934; Davern, T.J., et al., Drug-induced liver injury in clinical trials: as rare as hens' teeth, Am. J. Gastroenterol., 2009; 104(5):1159-1161; Lee, W.M., Davern, T.J., et al., Intravenous NAcetylcysteine Improves Transplant-Free Survival in Early State Non-Acetaminophen Acute Liver Failure, Gastroenterology, 2009, 137:856-864; Davern, T.J., Drug-Induced Liver Disease, Clin. Liver Dis., 2012, 16:231-245; Davern, T.J., Concepts in Drug-Induced Liver Disease, AGA Perspectives, 2012 May 23; Holt, E.W., Davern, T.J., et al., Acute Liver Failure Due to Acetaminophen Poisoning in Patients with Prior Weight Loss Surgery: A Case Series, J. Clin. Gastroenterol., 2014 Dec. 30 [Epub ahead of print]. See also T. Davern Dep., Mar. 28, 2015 at 31-35 (Doc. No. 155, Ex. 3).

"causation assessment methodology" he uses in this case. He wrote a book chapter called "Drug-Induced Liver Disease" at the request of McNeil's expert, Steven Flamm, M.D.[12]

II. Dr. Davern's General Causation Methodology is Reliable[13]

Dr. Davern opines that acetaminophen-induced livery injury can occur at or near 4 grams—the daily recommended dose of acetaminophen at the time of the decedent's death.[14] Dr. Davern was of this opinion prior to this litigation; he has routinely limited his patients to only 2 grams of acetaminophen a day.[15] He explained that certain factors enhance susceptibility to acetaminophen poisoning: chronic alcohol use, female gender, chronic ingestion of certain drugs, fasting/malnutrition, and/or gastric bypass surgery.[16]

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[12] See S. Flamm Dep., May 5, 2015 at 32-34 (Doc. No. 155, Ex. 9); T. Davern Dep., Mar. 28, 2015 at 37-39 (Doc. No. 155, Ex. 3).

[13] The defendants claim Dr. Davern's supplemental report was untimely. This report was served in response to their expert reports, which were given to Dr. Davern only hours before his deposition (as shown by the deposition testimony). See T. Davern Dep., Mar. 28, 2015 at 18-22 (Doc. No. 155, Ex. 3). The defendants' point is of no consequence.

[14] See T. Davern Expert Report, Feb. 16, 2015 at 5-6 (Doc. No. 155, Ex. 1).

[15] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 2 (Doc. No. 155, Ex. 2)("I have long limited the exposure of my patients to no more than 2 grams a day…"); T. Davern Dep., Mar. 28, 2015 at 105-09 (Doc. No. 155, Ex. 3).

Defendants' experts, Drs. Brown and Flamm also limit their patients to 2-4 grams a day. See R. Brown Dep., Apr. 30, 2015 at 72-73 (Doc. No. 155, Ex. 8)("I tell them to take no more than six or eight regular-strength tablets in a day, knowing that they'll take more….It's neigh on 2 grams [daily]."); S. Flamm Dep., May 5, 2015 at 168-69 (Doc. No. 155, Ex. 9)(explaining why he only recommends that patients take a maximum of 3 or 4 grams of Tylenol a day but advises them that this is the upper limit on what should be taken because he recognizes the likely risk of patients taking too much).

[16] See also T. Davern Dep., Mar. 28, 2015 at 330-31, 388-89 (Doc. No. 155, Ex. 3).

The defendant argue that Dr. Davern's opinion regarding malnutrition as a risk factor of acetaminophen-induced liver failure is scientifically unsound because he did not consider one article which contradicts his point. See Lauterburg, Bernhard, Analgesics and Glutathione, Am. J. Therapeutics, 9, 225-231 (2002)(Doc. No. 126, Ex. E). The article written in 2002 is a review of available literature on analgesics and glutathione. The author concludes from his review of the literature on fasting that "there is no convincing evidence that fasting enhances the toxicity of paracetamol [acetaminophen] in humans as reviewed by Prescott." Id. at 228-29. This article is not a study or a peer-reviewed case series. The fact that Dr. Davern does not address it and was not aware of it does not require his opinion to be excluded.

He also noted that not all the risk factors which could cause acetaminophen-induced liver injury are known, making a "wide margin of safety" (i.e., the difference between a safe dose and a toxic dose) important for everyone.[17] In making his determination, he relied on the available information on this subject area—case series, case reports, clinical trials, FDA documents, animal studies—and his own clinical experience.[18]

a. Lack of Epidemiological and Case-controlled Studies Does Not Render Opinion Unreliable[19]

The defendants argue that Dr. Davern's general causation opinion about the risk of acetaminophen-induced ALF at recommended doses is flawed because it is not supported by statistically-significant data.[20]

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[17] See T. Davern Expert Report, Feb. 16, 2015 at 5-6 (Doc. No. 155, Ex. 1); T. Davern Addendum to Expert Report, Apr. 27, 2015 at 3 (Doc. No. 155, Ex. 2).

The defendants also make an implicit Rule 403 argument, claiming testimony about fasting, malnutrition, and gastric bypass as risk factors will be a waste of time. I see nothing in the record to support this argument. The information being presented by the experts on this point is highly probative and relevant to this case.

[18] See T. Davern Dep., Mar. 28, 2015 at 53-57 (Doc. No. 155, Ex. 3).

[19] The defendants also claim Dr. Davern's reliance on a memorandum issued in 2007 by the American Association for the Study of Liver Disease (AASLD) is inappropriate because the memorandum was not peer-reviewed and some of its recommendations were rejected by the FDA. The AASLD is the leading organization of doctors and specialists on the study of liver disease in the United States. The information contained in this document is entirely relevant to Dr. Davern's opinion. I see no problem with Dr. Davern relying on the 2007 document—along with other available information—in forming his opinions. See Heller v. Shaw Industries, 167 F.3d 146, 155 (3d Cir. 1999)("Given the liberal thrust of the Federal Rules of Evidence, the flexible nature of the Daubert inquiry, and the proper roles of the judge and the jury in evaluating the ultimate credibility of an expert's opinion, we do not believe that a medical expert must always cite published studies on general causation in order to reliably conclude that a particular object caused a particular illness…. To so hold would doom from the outset all cases in which the state of research on the specific ailment or on the alleged causal agent was in its early stages, and would effectively resurrect a Frye-like bright-line standard, not by requiring that a methodology be 'generally accepted,' but by excluding expert testimony not backed by published (and presumably peer-reviewed) studies. We have held that the reliability analysis applies to all aspects of an expert's testimony: the methodology, the facts underlying the expert's opinion, the link between the facts and the conclusion, et alia.").

[20] The defendants argue that Dr. Davern's methodology is flawed because he did not look for statistically significant associations between substance exposure and injury and then apply the Bradford-Hill method—a set of nine guidelines to evaluate scientific data to determine causation. The Bradford-Hill methods, enunciated by Sir Austin Bradford Hill in a 1965 speech before the Royal Society of Medicine, includes a collection of "nine different

The Fourth Circuit addressed this exact same argument by the defendants in a similar case decided over twenty years ago. In Benedi v. McNeil, a jury found that the defendants failed to warn consumers about the risk of liver damage when acetaminophen was taken with alcohol. Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378, 1381 (4th Cir. 1995).[21] On appeal, McNeil argued that Benedi's experts should have been excluded because they "did not rely upon epidemiological data in formulating their opinions." Id. at 1384. The Fourth Circuit rejected this argument:

> [W]e do not read Daubert as restricting expert testimony to opinions that are based solely upon epidemiological data. Daubert merely requires that the expert testimony be both relevant and reliable; and Daubert clearly vests

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viewpoints" from which to "study association before we cry causation." Hill, A.B., The Environment and Disease: Association or Causation?, PROC. R. SOC. MED., 58(5):295–99 (May, 1965). These nine guidelines are: 1) the strength of the association; 2) consistency of the association; 3) specificity or whether there are multiple causes of a condition; 4) the temporal relationship between a condition followed the exposure to the agent; 5) biological gradient or the existence of a dose-response relationship; 6) how plausible the association is biologically; 7) whether the association is "coherent" with (i.e., does not seriously conflict with) generally known facts of the natural history and biology of the disease; 8) does experimentation—removing the causative agent—improve the condition; and 9) analogy. Id. See also In re Seroquel Products Liability Litigation, No. 6:06–md–1769–Orl–22DAB, 2009 WL 3806435, at *5, n. 5 (M.D. Fla. Jun. 23, 2009).

The defendants' interpretation of the type of association needed before using Bradford-Hill appears to be overstated. There is nothing to say that a statistically-significant association must be found before applying the methodology. See In re: Lipitor (Atorvastatin Calcium) Marketing, Sales Practices and Products Liability Litigation, --- F.Supp.3d ----, MDL No. 2:14–mn–02502–RMG, 2016 WL 1251828, at *2 (D.S.C. Mar. 30, 2016)("Randomized, double-blind, clinical trials are the 'gold standard' for determining whether an association exists. However, the Reference Manual on Scientific Evidence recognizes that observational studies can be sufficient to establish an association.")(citation omitted); Federal Judicial Center, Reference Manual on Scientific Evidence, at 598-99 (3d ed. 2011)(recognizing that an association is needed first to apply Bradford-Hill but not a statistically significant one); id. at 217-18 (recognizing the role of observational studies in establishing causation). The case the defendants cite for this argument is unpersuasive and/or distinguishable from this case. See In re Zoloft (Sertraline Hydrocholoride) Products Liability Litig., 26 F. Supp. 3d 449, 456 (E.D. Pa. 2014)(excluding expert opinion on teratogenicity, not drug-induced liver injury, because expert failed to follow generally accepted method in that field). I find nothing that requires the plaintiff's expert to use the methodology, as prescribed by the defendants.

[21] The defendants argue that reliance on Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378 (4th Cir. 1995), is misplaced because case reports in that action were only admissible to show notice, not proof of causation. It is the defendants' argument that is misplaced. In Benedi, the Fourth Circuit found that the district court did not err in admitting the case reports themselves into evidence, though they may be considered hearsay, because they were used to show notice. Id. at 1385-86. The court did not address whether reliance on case reports by experts in forming causation opinions was appropriate. Whether an expert can rely on case reports or whether a court can admit the case reports themselves into evidence are two entirely different questions. See FED. R. EVID. 703.

> the district courts with discretion to determine the admissibility of expert testimony. Under the Daubert standard, epidemiological studies are not necessarily required to prove causation, as long as the methodology employed by the expert in reaching his or her conclusion is sound.

Id. See also id. at 1384-85. While epidemiological studies can be valuable evidence of causation, they are not a pre-requisite for products liability causation expert testimony in this Circuit.[22] The defense experts admit that having case-controlled epidemiological data is not a requirement in finding causation for drug-induced liver injuries.[23]

In this case especially, epidemiological studies and/or statistically-significant clinical evidence would be difficult to obtain. Drug-induced ALF and severe liver injury are rare.[24] Case-controlled epidemiologic studies of rare diseases, such as ALF, with control groups are difficult to perform. Drug-induced

[22] See Wolfe v. McNeil-PPC, Inc., No. 07–348, 2011 WL 1673805, at *15 (E.D. Pa. May 4, 2011)(rejecting similar argument from McNeil in Motrin products liability action); Lanzilotti by Lanzilotti v. Merrell Dow Pharmaceuticals Inc., No. 82–0183, 1986 WL 7832, at *2 (E.D. Pa. Jul 10, 1986)("We note also that it has not been declared in this circuit that epidemiological studies are an indispensable element in the presentation of a prima facie drug product liability case, or that such studies must be the sole basis for expert opinion."); Mazur v. Merck & Co., Inc., 742 F.Supp. 239, 264 (E.D. Pa. 1990)(same). See also Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 449 (W.D. Pa. 2003)(discussing the value of epidemiological studies).

[23] See R. Brown Dep., Apr. 30, 2015 at 106-07 (Doc. No. 154, Ex. 3)("Q. My question is very specific, sir. My question is, is there a requirement in any of the peer-reviewed medical literature that before a drug can be ruled in as a potential hepatotoxic drug that there must be a case-controlled epidemiologic study?…A. The answer is, you have to have some data. What form that data takes varies, based upon the drug you're studying and what you're trying to assess. You have to have reliable data. And that reliable data can come from a number of sources. If you have randomized controlled clinical trial data, you don't have need much else. If you're requiring lower -- the way we grade data is you have a quality of the data and a confidence in the data, and then you come up with a strength of the recommendation. And that's a -- that was not a standard process in 1990 and 2000 when many of these articles were done, but it is the standard now. And so the higher the quality of the evidence, the fewer studies you need. The lower the quality of the evidence, the -- either you need stronger data or more research.") and at 107-109; S. Flamm Dep., May 5, 2015 at 97 (Doc. No. 154, Ex. 4)("Q. Okay. And there is no requirement in the causation algorithm that there be an epidemiologic study that would demonstrate a statistically significant 2.0 relative risk to a P-value of .05 standard epidemiologic association in order to rule in a drug as a potential cause for acute liver failure or DILI. True? A. Yes. Again, it's not a requirement, but for you to make a very good clinical decision and really understand an interaction with a particular patient and a product, you have to have some level of comfort in the data that are behind it.") and at 98.

[24] Dr. Davern also explained that death resulting from ALF is rare because patients often receive transplants. See T. Davern Dep., Mar. 28, 2015 at 324-25 (Doc. No. 155, Ex. 3).

ALF is unlikely to ever be seen in a human prospective placebo-controlled clinical trial, which studies a small number of patients.[25] Because of the rarity of drug-induced ALF, randomized placebo-controlled clinical trials would not necessarily establish a connection between acetaminophen and ALF.[26]

The experts in this case recognize that the types of studies the defendants claim are needed to make an opinion reliable—human prospective placebo-controlled clinical trials—are not feasible or ethical.[27] During his deposition, Dr. Anthony Temple, former Vice President of Medical Affairs at McNeil, admitted that McNeil consulted with epidemiologists to design a statistically-significant controlled study which would prove or disprove acetaminophen-induced ALF; they found such a study was not feasible and/or was too expensive to conduct.[28]

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[25] See Davern, T.J., et al, Drug-Induced Liver Injury in Clinical Trials: As Rare as Hen's Teeth (editorial), Am. J. Gastroenterol., 2009: 104: 1159-1161 (Doc. No. 154, Ex. 8); T. Davern Dep., Mar. 28, 2015 at 115-16, 119-26, 141, 144 (Doc. No. 155, Ex. 3).

[26] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 3 (Doc. No. 155, Ex. 2). See also A. Temple Dep., Mar. 20, 2014 at 91, 100, 185-86 (Doc. No. 154, Ex. 10).

[27] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 3-4 (Doc. No. 155, Ex. 2); T. Davern Dep., Mar. 28, 2015 at 121 (Doc. No. 155, Ex. 3).

See also N. Kaplowitz Dep., Jun. 3, 2014 at 138-42, 164, 214-15 (Doc. No. 154, Ex. 9)(Lyles Deposition) and at 139 ("I mean, there's no -- first of all, there is no scientific evidence that it does not because the studies are not powered to exclude it. And so, as one always has to do in the setting of rare events, is you have to see an accumulation of rare events. If this happened once in history, you know, one case report in the world's literature, obviously -- or two, even – we wouldn't be sitting here. But there are -- there's enough smoke here, enough case reports, coupled with all the other things that I've just been talking about that I won't repeat that I don't agree with."); S. Flamm Dep., May 5, 2015 at 94, 96-98 (Doc. No. 155, Ex. 9)(admitting that he cannot name one hepatotoxic drug which has statistically significant proof to show liver injury causation); R. Brown Dep., Apr. 30, 2015 at 105-09 (Doc. No. 154, Ex. 3)(same) and at 209-230 (Doc. No. 155, Ex. 8); A. Temple Dep., Mar. 20, 2014 at 84-85 (Doc. No. 154, Ex. 10)("Q. And because it would be inappropriate and unethical to prospectively expose a patient to a drug with the intent of trying to measure harm? A. Well, yeah. That's been an issue with giving overdoses of acetaminophen, yes. You wouldn't do it -- if you knew that giving a drug in a certain dose produced harm, then you wouldn't want to give it to someone.").

[28] See A. Temple Dep., Mar. 20, 2014 at 91 (Doc. No. 154, Ex. 10)(under seal)("I don't think there was an easy way or even a way to look retrospectively. I mean, we just did another case series with -- he admitted that it's very hard

Like the Fourth Circuit, I find the defendants' argument unpersuasive.[29] Dr. Davern has extensive clinical experience treating patients with acetaminophen-induced liver injury. He has enrolled 300 patients in ALFSG studies. Most of them suffered from acetaminophen poisoning.[30] He has presented to the FDA Advisory Committees about unintentional acetaminophen-induced liver injury. As a leading expert in acetaminophen-induced liver injury, he relies on his own clinical experience and available research in rendering his opinions.[31] He weighs the "totality of the evidence"—acetaminophen

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to define ingestion of alcohol or fasting during this period of time. So his case series was what it was. So doing the kind of epidemiology series I think you're describing, we determined wasn't a feasible study, but we have evaluated whether to do that or not, yes."), at 100 ("[W]e talked -- we had talked with epidemiologists, and we had looked at that issue, and I don't know that they -- I don't recall them ever giving us an adequate proposal, but the answer is yes, we did talk to them about the dosing issues and about ways to conduct epidemiology studies."), and at 185-86 ("McNeil has not done an epidemiology study that way because we couldn't find a way to conduct that trial.").

I also note that two different databases (the ALFSG and FDA databases) showed a risk in some people at 4 grams and that the median daily dose for liver injury was 5-7 grams a day. FDA Working Group Report (2008) at 11, n. 41 (Doc. No. 155, Ex. 24).

[29] I note that the way acetaminophen has been regulated—having been on the market, grandfathered in under the monograph system, and never issued a final monograph—may also explain why this type of research has never been conducted. Unlike other drugs, no pre-marketing research was conducted on acetaminophen to determine its adverse effects. In addition, while acetaminophen manufacturers are encouraged to explore reports of adverse events, they were not necessarily required to perform post-marketing research by regulation. See 21 C.F.R. § 330.12(c) (explaining how manufacturers of drugs with a Tentative Final Monograph are "encouraged to perform studies to obtain adequate evidence of effectiveness" and make appropriate changes in labels and formulations "to bring the products into conformity with current medical knowledge and experience"). This unique regulatory scheme is one reason why expert opinions without epidemiological or statistically-significant data may also be appropriate in this case.

[30] Among these references, Dr. Davern's cites Larson, A.M., Davern, T.J., et al., Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, Hepatology, 2005 Dec: 42(6): 1364-1372 (Doc. No. 154, Ex. 22). The defendants filed a separate motion to exclude the use of this article. See Motion to Exclude Opinion Testimony of Timothy Davern based on Supplemental Data, Jan. 29, 2016 (Doc. No. 193). I denied that motion. See Memorandum and Order Denying Defendants' Motion to Exclude Plaintiff's Expert Testimony Based on Larson Article/ALFSG Data, Jul. 14, 2016 (Doc. No. 224, 225). I see nothing improper with how Dr. Davern has used the Larson article—along with his other evidence—in rendering his opinion.

[31] See, e.g., T. Davern Addendum to Expert Report, Apr. 27, 2015 at 4-9 (Doc. No. 155, Ex. 2); Watkins, P., et al., "Aminotransferase Elevations in Healthy Adults Receiving 4 grams of Acetaminophen Daily: A Randomized Controlled Trial," JAMA, 296:87-93, 2006 (Doc. No. 155, Ex. 14); Sabate, M., et al., Paracetamol in therapeutic dosages and acute liver injury: causality assessment in a prospective case series, BMC Gastroenterology, 2011, 11:80 (Doc. No. 155, Ex. 16); Kurtovic, J. and Riordan, S.M., Paracetamol-Induced Hepatoxicity at Recommended Doses, J. Internal Med., 2003 Feb.: 253(2):240-3 (Doc. No. 155, Ex. 19); Forget, P., et al., Therapeutic dose of

clinical trials, animal studies, numerous case reports and case series, and his own clinical experience—in rendering his opinion.[32] I see nothing wrong with his general causation methodology.[33]

b. Reliance on the Watkins study is Appropriate

The defendants argue the Dr. Davern's reliance on a study from 2006 authored by Dr. Paul Watkins is not appropriate because the article discusses elevated

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acetaminophen may induce fulminant hepatitis in the presence of risk factors: A report of two cases, B. J. Anesthesia, Vol. 103, Issue 6; 899-900, 2009 (Doc. No. 155, Ex. 20); FDA Working Group Report (2008)(Doc. No. 155, Ex. 24).

[32] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 2-7 (Doc. No. 155, Ex. 2). See also In re Levaquin Products Liab. Litig., No. MDL 08-1943 JRT, 2010 WL 8400514, at *4 (D. Minn. Nov. 8, 2010)("When courts allow expert testimony premised on animal studies, it is because human studies cannot be done for ethical reasons, or there is a reasonable basis to believe that the results from the animal studies can be reliably extrapolated to humans….Though courts should be cautious in presuming that findings derived from animal studies are applicable to humans, the applicability of animal studies is often appropriately explored during cross-examination.")(citations omitted).

[33] The defendants argue that Dr. Davern cannot rely upon information contained in a 2008 report from the FDA's Acetaminophen Hepatotoxicity Working Group because it is not peer-reviewed and does not offer information to support Dr. Davern's opinions. See FDA Working Group Report (2008)(Doc. No. 155, Ex. 24). This is a weak argument. See Heller v. Shaw Industries, 167 F.3d 146, 155 (3d Cir. 1999)("Given the liberal thrust of the Federal Rules of Evidence, the flexible nature of the Daubert inquiry, and the proper roles of the judge and the jury in evaluating the ultimate credibility of an expert's opinion, we do not believe that a medical expert must always cite published studies on general causation in order to reliably conclude that a particular object caused a particular illness…. To so hold would doom from the outset all cases in which the state of research on the specific ailment or on the alleged causal agent was in its early stages, and would effectively resurrect a Frye-like bright-line standard, not by requiring that a methodology be 'generally accepted,' but by excluding expert testimony not backed by published (and presumably peer-reviewed) studies. We have held that the reliability analysis applies to all aspects of an expert's testimony: the methodology, the facts underlying the expert's opinion, the link between the facts and the conclusion, et alia.").

I see nothing inherently unreliable in a report prepared by a group of scientists, who are experts in this area of study, coming together to discuss, discern, and analyze possible concerns on this topic. Not only was the document produced with input from experts on the topic of acetaminophen-induced liver injury, including ones working for the defendants, but it was also sponsored by the FDA. The fact that the national regulatory agency convened a group of experts to discuss the issue of acetaminophen-induced liver injury, to collectively present and analyze the available information about acetaminophen-induced liver injury, provides the document with the indicia of reliability required under Daubert.

The Working Group report stated that acetaminophen has a narrow therapeutic margin. It discussed cases of liver injury caused by acetaminophen at or near recommended doses. The Working Group considered ways to reduce the risk of unintentional overdose and liver injury to consumers, including decreasing the maximum daily dose from 4000 milligrams to 3250 milligrams. This information would be relevant to Dr. Davern's opinions.

aminotransferase levels, not ALF.[34] See Watkins, P., et al., "Aminotransferase Elevations in Healthy Adults Receiving 4 grams of Acetaminophen Daily: A Randomized Controlled Trial," JAMA, 296:87-93, 2006 (Doc. No. 155, Ex. 14).

The Watkins article found that some adults had developed abnormalities in liver enzymes (e.g., aminotransferases or ALTs) after taking recommended doses of acetaminophen.[35] ALF occurs when the liver is severely damaged. Elevated ALTs are markers of liver damage (i.e., liver cell death).[36] Increased ALTs do not necessarily lead

[34] They also point out the Watkins article's statements that "acetaminophen clearly has a remarkable safety record when taken as directed, and chronic treatment with 4 g daily has been confirmed to be safe." Watkins, P., et al., "Aminotransferase Elevations in Healthy Adults Receiving 4 grams of Acetaminophen Daily: A Randomized Controlled Trial," JAMA, 296:87-93, 93 (2006)(Doc. No. 155, Ex. 14). The mere fact that the article acknowledges that acetaminophen is typically safe at recommended doses does not mean that other findings in the article should be negated or reliance on the article is inappropriate.

[35] The defendants claim that Dr. Davern's general causation opinion is unreliable because he "cherry picked" evidence that would support his findings, while disregarding evidence that contradicted them. The defendants argue that Dr. Davern did not address studies conducted by McNeil and others, which contradicted the findings in Watkins. See Kuffner, E.K., et al., Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: a randomized, double-blind, placebo-controlled trial, Arch. Intern. Med., 2001, 161:2247-52 (Doc. No. 126, Ex. J); Kuffner, E.K., et al., The effect of acetaminophen (four grams a day for three consecutive days) on hepatic tests in alcoholic patients – a multicenter randomized study, BMC Medicine, 2007; 5:13 at 4. (Doc. No. 126, Ex. K); Temple, A. et al., Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Trial of the Long Term (6-12 Months) Safety of Acetaminophen in Adult Patients with Osteoarthritis, Clinical Therapeutics (2006)(Doc. No. 126, Ex. M). See also Heard at el., A randomized trial to determine the change in alanine aminotransferase during 10 days of paracetamol (acetaminophen) administration in subjects who consume moderate amounts of alcohol, Alimentary Pharmacology & Therapeutics (2007)(Doc. No. 126, Ex. L). This point goes to weight, not admissibility.

[36] See Davern, T., Book Chapter: "Drug Induced Liver Disease" In Approach To Consultations For Patients With Liver Disease, Flamm, S.L. guest editor, May 2012, Vol. 16, No. 2, 231-244, 232 (Doc. No. 155, Ex. 4)("Acute hepatocellular injury is caused by injury primarily to the hepatocytes and is characterized be elevated levels of [liver chemistries reflecting injury].Severe hepatocellular injury may evolve into acute liver failure with hepatic synthetic dysfunction and hepatic encephalopathy, which carries a very poor prognosis and often requires a liver transplantation for survival."); T. Davern Dep., Mar. 28, 2015 at 101 (Doc. No. 155, Ex. 3)("The injury caused by acetaminophen is a spectrum. Some patients have mild, asymptomatic elevations of the serum aminotransferases with absolutely no symptoms or sequela, but there are other patients who have more severe liver injury. And, again, it is a continuum, with the far end being acute liver failure, the syndrome where there is not only severe injury, but liver failure with coagulopathy and mental status changes, hepatic encephalopathy.")

See also R. Brown Dep., Apr. 30, 2015 at 15 (Doc. No. 155, Ex. 8)("Q. Okay. Well, for acute liver disease, the range of liver disease is typically from asymptomatic elevations in liver enzymes all the way through acute liver failure and death. True? A. Well, asymptomatic elevations of liver enzymes may or may not be related to drug induced liver injury. And that's where many of these issues arise because patients who are ill can have injuries in the

to ALF.[37] However, elevated ALTs are one early indicator that ALF might occur.[38] The defendants fail to acknowledge the fact that the Watkins study was stopped early because the authors were concerned about the harm being caused to study participants.[39] It would not have found ALF because inducing ALF—a life threatening condition—would have been unethical. I see no problem with Dr. Davern's use of the Watkins data to support his opinions, along with the many other sources he cites.[40]

c. Dr. Davern's Use of Case Reports is Appropriate in this Case

The defendants argue that Dr. Davern cannot use case reports to establish causation.[41] It is true that case reports and anecdotal evidence alone may not be sufficient

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liver enzymes and they may or may not have drug induced liver injury. But drug induced liver injury does have a spectrum from mild to severe, including acute liver failure.").

[37] See T. Davern Dep., Mar. 28, 2015 at 132 (Doc. No. 155, Ex. 3).

[38] See T. Davern Dep., Mar. 28, 2015 at 132, 159-61 (Doc. No. 155, Ex. 3).

Dr. Temple also admitted that looking at elevated ALTs is one way to study the risk of ALF. See A. Temple Dep., Mar. 20, 2014 at 85 (Doc. No. 154, Ex. 10)("Q. Right. So the way in which you study risk in clinical trials is to look for surrogates for risk. Oftentimes you look for laboratory abnormalities. If there happens to be a patient reaction during the clinical trial, you look for measurements of blood pressure, liver function tests, those kinds of things as a predictor, potential predictor of clinical problems when a drug is more widely used, true? A. You can do that, yes.").

[39] The defendants also do not recognize McNeil's own research using elevated ALTs and ASTs in patients taking 4 grams. See McNeil chart, Summary of Peak Lab Values Post-Baseline, Jul. 6, 2012 (Doc. No. 155, Ex. 15); T. Davern Addendum to Expert Report, Apr. 27, 2015 at 5 (Doc. No. 155, Ex. 2)(citing Ex. 15).

[40] The defendants also claim Dr. Davern's reliance on data from the Acute Liver Failure Study Group (ALFSG), including Larson, A.M., Davern, T.J., et al., Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, Hepatology, 2005 Dec: 42(6): 1364-1372 (Doc. No. 154, Ex. 22)(i.e., the "Larson article"), is not appropriate because this data is nothing more than case reports. The defendants filed a separate motion regarding the admissibility and validity of the ALFSG data. See Doc. No. 193. I explain in my decision on that motion why the ALFSG data is admissible and can be relied upon by experts in the field. See Memorandum and Order Denying Defendants' Motion to Exclude Plaintiff's Expert Testimony Based on Larson Article/ALFSG Data, Jul. 14, 2016 (Doc. No. 224, 225). I see no problems with the way Dr. Davern has used this data in forming his opinions. See T. Davern Dep., Mar. 28, 2015 at 119-121 (Doc. No. 155, Ex. 3).

[41] Along the same lines, the defendants argue that Dr. Davern's opinion that acetaminophen-induced ALF can occur at 4 grams is not admissible because it relies on data from the Acute Liver Failure Study Group (ALFSG)—an "uncontrolled" registry of case reports. To support this opinion, the defendants cite Ratner v. McNEIL-PPC, Inc., 91 A.D.3d 63 (N.Y. App. Div. Nov. 22, 2011). This precedent is non-binding and unpersuasive. I further address why

support for a causation opinion. See, e.g., Wade-Greaux v. Whitehall Labs., Inc., 874 F. Supp. 1441, 1483 (D.V.I. 1994)("…anecdotal human data, whether from published case reports, DERs or other litigation, have inherent biases that make them unreliable."). However, case reports considered in conjunction with other evidence may be an appropriate basis for an expert's causation opinion.[42] Dr. Davern does not rely solely on case reports in rendering his opinion. The case reports and case series he does cite also include controls on the information analyzed, which enhance their reliability.[43]

In addition, case reports and case series are the types of information on which DILI experts rely. See FED. R. EVID. 703; Wolfe v. McNeil-PPC, Inc., No. 07–348, 2012

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the ALFSG data is more than an "uncontrolled" registry of case reports in my decision on the admissibility of that data. See generally Memorandum and Order Denying Defendants' Motion to Exclude Plaintiff's Expert Testimony Based on Larson Article/ALFSG Data, Jul. 14, 2016 (Doc. No. 224, 225).

[42] See Wolfe v. McNeil-PPC, Inc., No. 07–348, 2012 WL 38694, at *3 (E.D. Pa. Jan. 9, 2012)("As for the use of AERs as bases for expert testimony, this Court has previously ruled that expert testimony that relies, in part, on case reports to establish causation satisfies the requirements of Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). See Wolfe v. McNeil–PPC, Inc., No. 07–348, 2011 WL 1673805, at *5 (E.D. Pa. May 4, 2011). The Court reiterates its conclusion that, because plaintiff's experts 'did not solely rely on case reports in forming their opinions on causation but used them to supplement their extensive review" of other evidence, such testimony is admissible."); Wolfe v. McNeil–PPC, Inc., No. 07–348, 2011 WL 1673805, at *5 (E.D. Pa. May 4, 2011)("In this case, the three doctors did not solely rely on case reports in forming their opinions on causation but used them to supplement their extensive review of plaintiff's medical records and deposition testimony of plaintiff's treating physicians. As with defendants' other objections, the three doctors' use of case studies in reaching their conclusion affects only the weight to be given their testimony, not its admissibility. Thus, the proposed testimony of the three doctors is based on sufficiently reliable methods."); Schedin v. Ortho–McNeil–Janssen Pharm., Inc., 808 F.Supp.2d 1125, 1139 (D. Minn. 2011)(explaining that AERs are commonly used by experts to determine causation in conjunction with other evidence), rev'd in part on other grounds, In re Levaquin Prods. Liab. Litig., 700 F.3d 1161 (8th Cir. 2012).

[43] See Caraker v. Sandoz Pharm. Corp., 172 F.Supp.2d 1046, 1050 (S.D. Ill. 2001)(explaining how "an overwhelming amount" of case reports/series with appropriate controls, analysis of alternative causes, temporal proximity may be a reliable basis for expert opinion). See also Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 537-44 (W.D. Pa. 2003)(finding case reports to be unreliable and "unscientific" bases for causation opinion because are unpublished, not peer-reviewed, did not consider alternative causes, patients' medical history, etc.); McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1250 (11th Cir. 2005)(explaining that anecdotal information "without any medical controls or scientific assessment" is unreliable basis for expert opinion); Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1211 (10th Cir. 2002)(finding that exclusion of opinions based on case reports with little information about medical history appropriate but that case reports with more detailed information may be reliable source of expert opinion).

WL 38694, at *3 (E.D. Pa. Jan. 9, 2012); FDA Working Group Report (2008) at p. 11, n. 41 (Doc. No. 154, Ex. 30)(explaining how members of the working group looked at two different databases of case reports/adverse event reports (AERs) in finding that there is a risk of liver injury for some people at 4 grams).[44] As explained above, epidemiological or case-controlled studies for acetaminophen-induced liver injuries are not available. In the absence of epidemiological data, case reports and case series may be valuable sources of information for DILI experts, doctors, and scientists in determining causation.[45]

III. Dr. Davern's Specific Causation Opinion is Reliable[46]

After reviewing Ms. Hayes' medical records, Dr. Davern opined that Ms. Hayes died of acetaminophen-induced ALF after taking recommended doses of Tylenol. He ruled out alternative causes and noted that Ms. Hayes' biochemical patterns were consistent with acetaminophen-induced ALF.[47] He noted that her prior gastric bypass surgery was a risk factor.

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[44] Whether the case reports themselves may be admissible or disclosed to the jury is a separate question, which I will defer until I see how they may be used at trial. See FED. R. EVID. 703 ("An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed. If experts in the particular field would reasonably rely on those kinds of facts or data in forming an opinion on the subject, they need not be admissible for the opinion to be admitted. But if the facts or data would otherwise be inadmissible, the proponent of the opinion may disclose them to the jury only if their probative value in helping the jury evaluate the opinion substantially outweighs their prejudicial effect."); Wolfe v. McNeil-PPC, Inc., No. 07–348, 2012 WL 38694, at *3 (E.D. Pa. Jan. 9, 2012).

[45] See, e.g., T. Davern Addendum to Expert Report, Apr. 27, 2015 at 4 (Doc. No. 155, Ex. 2)(explaining the usefulness of case reports in DILI causation analysis); N. Kaplowitz Dep., Jun. 3, 2014 at 134-136, 139, 158, 194, 213 (Doc. No. 154, Ex. 9)(Lyles Deposition); Davern, T.J., et al., Drug-Induced Liver Injury in Clinical Trials: As Rare as Hen's Teeth (editorial), Am. J. Gastroenterol., 2009: 104: 1159-1161 (Doc. No. 154, Ex. 8)(explaining how multi-center reporting is important to understanding DILI); FDA Working Group Report (2008) at 3-5, 11, n. 41 (Doc. No. 154, Ex. 30).

[46] See T. Davern Expert Report, Feb. 16, 2015 at 6-9 (Doc. No. 155, Ex. 1); T. Davern Addendum to Expert Report, Apr. 27, 2015 at 8-11 (Doc. No. 155, Ex. 2). See also T. Davern Dep., Mar. 28, 2015 at 82-92, 179-309, 378-80 (Doc. No. 155, Ex. 3).

[47] See T. Davern Dep., Mar. 28, 2015 at 195-234, 239-271 (Doc. No. 155, Ex. 3).

Dr. Davern uses a "causality assessment methodology" (CAM) in rendering his specific causation opinion.[48] This is the same methodology Dr. Davern uses when treating patients. While there are variations among CAM tools, at the core of this methodology is a "differential assessment." DILI causality assessments consider a combination of factors, including: temporal associations, the rate of improvement after cessation of the drug, the definitive exclusion of alternative causes, and the "signature" of the drug as revealed in clinical trials and experience.[49] This "science of [DILI] causality assessment" has been published by DILI experts in various forms since the 1980s.[50]

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[48] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 2-3 (Doc. No. 155, Ex. 2)

The defendants do not dispute that CAM is a reliable methodology. Defendants' Reply, Doc. No. 172 at 11. They argue that Dr. Davern has applied the methodology incorrectly. How he misapplied the CAM, in their view, is unclear. I see nothing in Dr. Davern's reports to indicate a misapplication of this methodology.

[49] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 2-3 (Doc. No. 155, Ex. 2); Davern, T., Book Chapter: "Drug Induced Liver Disease" In Approach To Consultations For Patients With Liver Disease, Flamm, S.L. guest editor, May 2012, Vol. 16, No. 2, 231-244, 237-39 (Doc. No. 155, Ex. 4). See also Kaplowitz N., Causality Assessment verses Guilt by Association in Drug Hepatoxicity, Editorial, Hepatology, 33:308-310, 2001 (Doc. No. 154, Ex. 11); R. Brown Dep., Apr. 30, 2015 at 103-05 (Doc. No. 154, Ex. 3); S. Flamm Dep., May 5, 2015 at 69, 138-140 (Doc. No. 155, Ex. 9).

[50] See, e.g., Maria, V. & Victorino, R., Development and Validation of a Clinical Scale for the Diagnosis of Drug Induced Hepatitis, Hepatology, Vol. 26; 664-669, 1997; Aithal, G., et al., Clinical Diagnostic Scale: A Useful Tool in the Evaluation of Suspected Hepatotoxic Adverse Drug Reactions, J. Hepatology, 2000:33; 949-953; Danan G., et al., Causality Assessment of Adverse Reactions to Drugs – I. A Novel Method Based on the Conclusions of the International Consensus Meetings: Application to Drug Induced Liver Injuries [RUCAM], J. Clin. Epidemiol., 1993; 46:1323-1330; Benichou, C., et al., Criteria of Drug Induced Liver Disorders: Report of an International Consensus Meeting [CIOMS], J. Hepatol.,1990:11:272-276; Lucena, M., et al., Comparison of Two Clinical Scales for Causality Assessment in Hepatotoxicity, Hepatology, 2001: 33:123-130; Lee, W.M., Assessing Causality in Drug Induced Liver Injury, J. Hepatology, 2000, 33:1003-1005; Kaplowitz, N., Causality assessment versus guilt-by-association in drug hepatotoxicity, Hepatology, Vol. 33, No. 1, 308-10, 2001; Davern, T., Drug-Induced Liver Disease, in Clinics in Liver Disease, Vol. 13, No. 2, May 2012, 231-239 ("Diagnosis of DILI: Causality Assessment"]; Causality Assessment in Drug Induced Liver Injury, Presentation at the FDA, PhRMA, ASSLD Symposium by Robert J. Fontana, M.D. (Jan. 28, 2005).

a. Use of the Holt Study in Rendering his Specific Causation Opinion

The defendants argue that Dr. Davern's general causation opinion that gastric bypass surgery may be a risk factor for acetaminophen-induced acute liver failure (ALF) is not reliable because Dr. Davern only cites one study he published in 2014. See E. Holt, et al., "Acute Liver Failure Due to Acetaminophen Poisoning in Patients With Prior Weight Loss Surgery: A Case Series," J. Clin. Gastroenterol., Vol. 00, No. 00, 1-4 (2014)(Doc. No. 154, Ex. 29). This study was published several years after the decedent's death. Dr. Davern's deposition testimony, however, makes clear that his opinion about gastric bypass surgery ties into his opinions about fasting and malnutrition.[51] He bases his opinions not simply on the findings in the Holt study, but also his understanding of how fasting and malnutrition—and, in turn, gastric bypass surgery—can affect glutathione levels.[52] Glutathione is necessary to neutralize toxins caused by acetaminophen.

The defendants also claim the Holt study cannot be relied on because it does not report dosing. Dr. Davern offers other evidence to support his opinion

[51] See T. Davern Dep., Mar. 28, 2015 at 100-03, 185-85, 235-37, 343-45 (Doc. No. 155, Ex. 3).

The defendants claim that Dr. Davern offers no evidence that Ms. Hayes was malnourished. Dr. Davern indicates that Ms. Hayes was vomiting, dehydrated, and experiencing hypoglycemia. See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 2-7 (Doc. No. 155, Ex. 2). See also T. Davern Dep., Mar. 28, 2015 at 393 (Doc. No. 155, Ex. 3). This information is enough for him to opine about Ms. Hayes' nutritional state. Any flaws in his reasoning can be brought out on cross-examination.

[52] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 6-7 (Doc. No. 155, Ex. 2); T. Davern Expert Report, Feb. 16, 2015 at 5-6 (Doc. No. 155, Ex. 1). See also Kurtovic, J. and Riordan, S.M., Paracetamol-Induced Hepatoxicity at Recommended Doses, J. Internal Med., 2003 Feb; 253(2):240-3 (Doc. No. 155, Ex. 19)(as support for liver injury with fasting and recommended doses); Forget, P., et al., Therapeutic dose of acetaminophen may induce fulminant hepatitis in the presence of risk factors: A report of two cases, B. J. Anesthesia, Vol. 103, Issue 6; 899-900, 2009 (Doc. No. 155, Ex. 20)(as support for liver injury with recommended doses and gastric bypass).

that acetaminophen-induced ALF can occur at recommended doses.[53] That evidence is enough to support that part of his opinion.

b. Dr. Davern's Discussion of Sepsis was Appropriate

The defendants argue that Dr. Davern's specific causation opinion is flawed because he didn't specifically note that he ruled out sepsis as an alternative cause. Only after he was served the defendants' expert reports did he address sepsis. Dr. Davern explained during his deposition why he did not even consider sepsis as an alternative cause before reading the defendants' expert reports—because it was "a far reach."[54] Dr. Davern has had considerable experience with sepsis, treating many patients with it during his career.[55] He explained in his response to defendants' expert reports that he "did not include sepsis in [his] initial report because there was no evidence [Ms. Hayes] had any type of significant infection at presentation, much less an infectious process that progressed or developed into sepsis."[56] He explained how her blood cultures and urine tests were negative, none of her treating physicians considered sepsis as a cause of death, that she did not present with an infection when she was in the hospital the week before

[53] See T. Davern Addendum to Expert Report, Apr. 27, 2015 at 6-7 (Doc. No. 155, Ex. 2)(noting a hospital case from 2009 of acetaminophen poisoning related to gastric bypass).

[54] See T. Davern Dep., Mar. 28, 2015 at 21-22 (Doc. No. 155, Ex. 3), at 351 ("Again, most patients with acetaminophen poisoning that die, die from multiorgan failure. And most of those patients have a positive blood culture before -- or many of them have positive blood cultures or other cultures before death. The diagnosis on the death certificate is still acute liver failure from acetaminophen poisoning, but they had sepsis as well. Again, the two -- the two aren't mutually exclusive, and sepsis complicates acute liver failure frequently. I just don't think in this case sepsis explains her presentation, and I think that, despite a fairly intensive investigation with cultures and imaging, et cetera, that there wasn't convincing evidence in this patient of sepsis."), and at 195-217, 257-58, 266-67, 271, 284, 305-06, 351.

[55] T. Davern Addendum to Expert Report, Apr. 27, 2015 at 7 (Doc. No. 155, Ex. 2).

[56] Id.

her death, and that she did not show other signs of sepsis (i.e., deeply jaundiced skin, elevated ammonia, etc.).[57] The defendants' argument is unpersuasive.

c. Use of McNeil's CAM Instrument

Lastly, the defendants argue that Dr. Davern's causality assessment of Ms. Hayes' case is flawed because he "relies upon a causality assessment form that is not generally accepted in the scientific community." In fact, the form Dr. Davern uses is the one *McNeil uses* in determining causality, as confirmed by Dr. Anthony Temple (former Vice President of Medical Affairs at McNeil) during his deposition.[58] This form was created with the assistance of Dr. Neil Kaplowitz, a leading DILI expert.[59] This argument borders on ridiculous. McNeil criticizes Dr. Davern for using a form McNeil has approved. McNeil's CAM assessment instrument—developed by a leading DILI expert for a leading producer of acetaminophen—shows all signs of being a reliable methodological tool for determining causation in this case.

IV. CONCLUSION

Overall, I find that Dr. Davern's opinions are reliable and appropriate under Daubert and the Federal Rules of Evidence. I will DENY the defendants' motion.

An appropriate Order follows.

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[57] Id. at 7-8.

[58] See A. Temple Dep., Mar. 20, 2014 at 310-13 (Doc. No. 155, Ex. 12).

[59] See N. Kaplowitz Dep., Apr. 21, 2015, at 310-312 (Doc. No. 154, Ex. 5)(Hayes Deposition); Doc. No. 154, Ex. 1 (under seal)(McNeil CAM assessment with emails between Kaplowitz and Temple).